When rats run, their gut bacteria rewrite the chemical conversation with the brain

Voluntary exercise reshapes gut microbiota and tryptophan metabolism, with consequences for the hippocampus, the brain's memory center

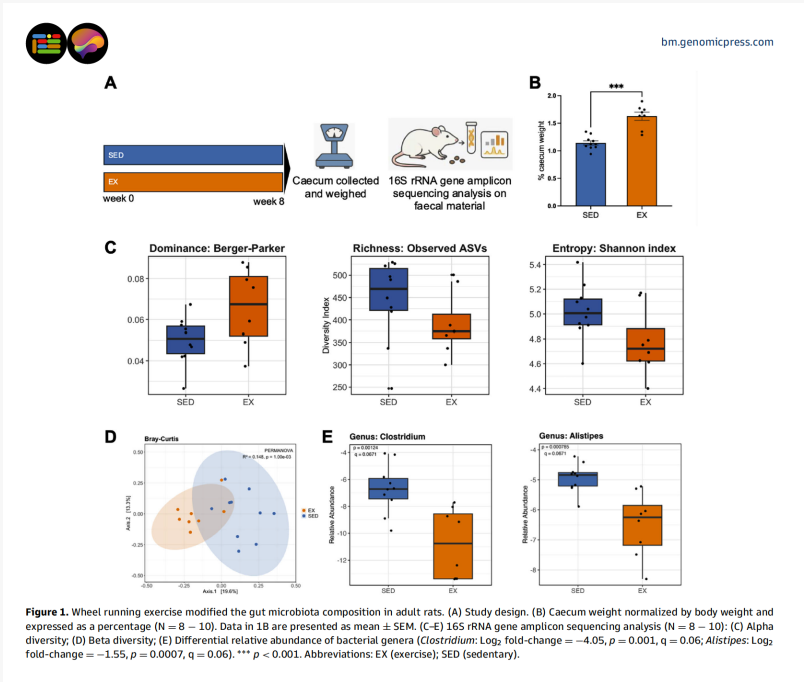

Figure 1. Wheel running exercise modified the gut microbiota composition in adult rats. (A) Study design. (B) Caecum weight normalized by body weight and expressed as a percentage (N = 8 – 10). Data in 1B are presented as mean ± SEM. (C–E) 16S rRNA gene amplicon sequencing analysis (N = 8 – 10): (C) Alpha diversity; (D) Beta diversity; (E) Differential relative abundance of bacterial genera (*Clostridium:* Log_2 fold-change = −4.05, $p = 0.001$, q = 0.06; *Alistipes:* Log_2 fold-change = −1.55, $p = 0.0007$, q = 0.06). *** $p < 0.001$. Abbreviations: EX (exercise); SED (sedentary).

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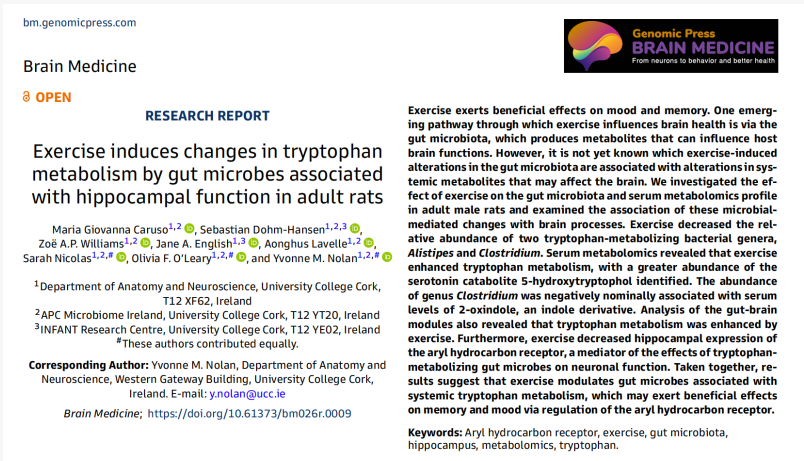

Exercise induces changes in tryptophan metabolism by gut microbes associated with hippocampal function in adult rats

CORK, COUNTY CORK, IRELAND, March 10, 2026 /EINPresswire.com/ -- Something happens when a rat starts running. Not just the obvious things, the faster heart, the warming muscles, the rhythmic percussion of paws against the wheel. Something quieter. Something that begins in the coiled darkness of the gut and travels, through blood and biochemistry, all the way to the hippocampus, that seahorse-shaped sliver of tissue where memories form and moods take root. A new study published in Brain Medicine, a Genomic Press journal, has begun to map that hidden journey, and what the researchers found suggests that exercise stimulates a molecular link between gut bacteria and the brain.

The research, led by Maria Giovanna Caruso and senior author Yvonne M. Nolan at the Department of Anatomy and Neuroscience, University College Cork, Ireland, along with co-senior authors Sarah Nicolas and Olivia F. O'Leary, examined what happens to the gut microbiota, circulating metabolites, and hippocampal gene expression when adult male Sprague-Dawley rats are given free access to a running wheel for eight weeks. The exercising animals ran an average of 5.24

> We observed exercise-driven changes in tryptophan-metabolizing gut bacteria, shifts in circulating metabolites, and reduced aryl hydrocarbon receptor expression in the dorsal hippocampus."
>
> *Professor Yvonne M. Nolan, University College Cork*

kilometers per day. Their sedentary counterparts did not have this opportunity. The differences that emerged were not dramatic in the way a broken bone is dramatic. They were subtle, layered, and potentially consequential.

The team discovered that exercise decreased the relative abundance of two bacterial genera, Alistipes and Clostridium, both of which are associated with tryptophan metabolism. Tryptophan is an essential amino acid and the precursor to serotonin, making it an important molecule in gut-to-brain signaling. Most tryptophan is metabolized in the liver via the kynurenine pathway. The remainder is broken down by gut microbes into tryptamine or various indole derivatives, some of which can cross the blood-brain barrier, or into serotonin, which, when produced in the gut, cannot.

That distinction matters because gut microbes may influence how tryptophan is distributed across competing metabolic pathways, including those relevant to brain function. By altering the composition of the microbiota, exercise may shift neuroactive signaling.

Using 16S rRNA gene amplicon sequencing of fecal material (a technique that identifies microbial communities by their genetic signatures), the researchers found that exercise increased microbial dominance (Berger-Parker index: $p = 0.05$) but not richness (Observed ASVs: $p = 0.18$), producing a decrease in overall entropy (Shannon index: $p = 0.05$). Beta diversity differed significantly between exercised and sedentary animals (Bray-Curtis PERMANOVA, $R^2 = 0.148$, $p = 0.001$). At the genus level, Clostridium showed a Log2 fold-change of −4.05 ($p = 0.001$, $q = 0.06$), and Alistipes a Log2 fold-change of −1.55 ($p = 0.0007$, $q = 0.06$). Exercise also increased caecum weight normalized by body weight, a finding the authors suggest may be associated with enhanced fermentation.

The researchers next performed untargeted serum metabolomics. Of 474 metabolites that met criteria for differential abundance testing, seven differed significantly between groups. Among them, the putative tryptophan derivative 5-hydroxytryptophol was enhanced in exercised rats ($\beta = 1.06$; $p < 0.05$; FDR = 0.01). This compound is a serotonin catabolite, produced when serotonin is metabolized via the reductive pathway rather than the more common oxidative route that yields 5-hydroxyindoleacetic acid. Its increased abundance in serum following exercise may reflect higher peripheral serotonin turnover, indicating a shift in one branch of tryptophan metabolism. The authors note a caveat: 5-hydroxytryptophol was identified at the lowest-confidence annotation level, level 3.

Pathway analysis of the differentially abundant metabolites supported the broader pattern. Among the top 10 significantly enriched pathways were tryptophan metabolism and

phenylalanine, tyrosine and tryptophan biosynthesis. The researchers also found a negative nominal association between the abundance of genus Clostridium and serum levels of 2-oxindole, an indole derivative ($\beta = -0.18$, $p < 0.05$, FDR = 0.2). That association did not remain significant after FDR correction, and the authors present it as suggestive rather than conclusive. But it points toward a possible mechanistic link between exercise-responsive gut microbes and circulating tryptophan metabolites.

Tryptophan derivatives such as indoles and oxindoles are ligands of the aryl hydrocarbon receptor, or AhR, a transcription factor that mediates the effects of tryptophan-metabolizing gut microbes on neuronal function. In the hippocampus, exercise reduced AhR transcript levels specifically in the dorsal region ($p = 0.05$), which is predominantly involved in memory-related processes. No significant change appeared in the ventral hippocampus, the region more closely linked to emotion. No statistically significant changes were detected in related transcripts, the aryl hydrocarbon receptor nuclear translocator (Arnt) or Cyp1a1, in either hippocampal region.

The dorsal hippocampus is the seat of spatial and contextual memory. The authors note that their results align with previous findings showing that the effects of exercise on behavior and hippocampal neurogenesis in adult male rats are distributed along the longitudinal axis, with the dorsal region being particularly susceptible to exercise-induced stimulation.

Analysis of gut-brain modules, functional units involved in gut-brain communication inferred from KEGG orthologs, reinforced the tryptophan thread. The researchers found significant changes in nine modules ($q < 0.2$), including an increase in acetate and glutamate synthesis and a decrease in GABA. Notably, the gut-brain module for tryptophan synthesis was enhanced by exercise. This inferred functional analysis suggests that exercise was associated not only with shifts in microbial composition, but also with changes in the metabolic response of the microbiome that may be relevant to neurochemistry.

"The fact that AhR expression was reduced specifically in the dorsal hippocampus, and not in the ventral hippocampus, is particularly interesting," said Olivia F. O'Leary, co-senior author and Professor at the Department of Anatomy and Neuroscience and APC Microbiome Ireland, University College Cork. "These two hippocampal subregions serve different functions. The dorsal hippocampus is more closely involved in memory, while the ventral hippocampus is more associated with emotion and anxiety. The regional specificity we observed raises the possibility that exercise-induced changes in gut-derived tryptophan metabolites may preferentially influence memory-related circuitry, though we would need behavioral data to confirm that."

The authors acknowledge that behavioral tests were not performed in the current study, and that confirming a correlation between changes in AhR expression and hippocampal-dependent behaviors would consolidate the functional role of the observed exercise-induced decrease in AhR expression in the dorsal hippocampus. They note that while AhR knockout in mice has shown the receptor negatively regulates hippocampal processes including adult hippocampal neurogenesis, AhR has also been implicated in detrimental effects on Alzheimer's disease

neuropathology, and that knockout models are not comparable with physiological responses to a stimulation such as exercise. They further acknowledge that these findings may not generalize to adult female rodents, extended age ranges, or diverse exercise paradigms.

The limited taxonomic resolution of 16S rRNA gene amplicon sequencing also constrains interpretation, as microbial species within the same genus may differentially contribute to metabolic functions. And the identification of 5-hydroxytryptophol at the lowest-confidence annotation level is a caveat the team presents with transparency.

"When we saw that both Alistipes and Clostridium, two genera with established roles in tryptophan metabolism, were significantly reduced by exercise, that was the moment the study began to take shape," said Maria Giovanna Caruso, first author and doctoral researcher at the Department of Anatomy and Neuroscience and APC Microbiome Ireland, University College Cork. "The serum metabolomics then showed us that tryptophan metabolism was indeed enhanced in the exercised animals, with 5-hydroxytryptophol, a serotonin catabolite, among the differentially abundant compounds. Connecting those microbial changes to circulating metabolites and then to a specific receptor in the hippocampus was what allowed us to propose this as an integrated gut-brain pathway responsive to exercise."

What remains is a picture of coherence. We have long known that exercise improves mood and sharpens memory. We have suspected for years that the gut microbiota plays a role in brain health. This study, conducted with careful methodology and appropriate restraint in its conclusions, provides a portrait of how these two truths may be connected. The gut is not merely digesting food. It is composing chemical letters to the brain. And exercise, it seems, changes the handwriting.

The research was funded by Research Ireland (formerly Science Foundation Ireland) under Grant Number SFI/FFP/6820. All animal procedures were performed under licenses issued by the Health Products Regulatory Authority of Ireland, in accordance with the European Communities Council Directive (2010/63/EU), and approved by the Animal Experimentation Ethics Committee of University College Cork.

For anyone who has ever felt clearer after a walk, calmer after a run, sharper after an hour on a bicycle, this study offers something quietly revolutionary: a molecular explanation that begins not in the muscles or the lungs but in the dark, crowded, astonishingly communicative world of the gut. The bacteria noticed you were moving. And they told your brain.

The peer-reviewed research article in Brain Medicine titled "Exercise induces changes in tryptophan metabolism by gut microbes associated with hippocampal function in adult rats" is freely available via Open Access, starting on 10 March 2026 in Brain Medicine at the following link: https://doi.org/10.61373/bm026r.0009

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